Supplementary Appendix. Estimation methods and calculations used to derive the tuberculosis care cascade in Zambia in 2018.

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Table 1. Overall TB Care Cascade in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. TB burden	72,495 (40,495 - 111,495)	100	WHO 2019 analysis of TB incidence in 2018 plus 50% of the number of undetected cases from 2017.[1]	• TB incidence, 2018 (all): 60,000 • TB incidence, 2017 (all): 61,000 • Case detection rate, 2017: 59.0% • Estimated undetected cases 2017: 24,990 • 50% of undetected cases who have not died/self-cured: 12,495
Gap 1	29,108 (0-66,777)	40.2	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	43,387 (95%CI: 42,390-44,718)	59.8	Add DS-TB and RR-TB cases that accessed TB testing (see Tables 2 and 3 for estimates).	• DS-TB: 42,477 (95%CI: 41,614-43,625) • RR-TB: 910 (95%CI: 776-1,093)
Gap 2	3,211 (95%CI: 2,262-4,506)	4.4	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed	40,176 (95%CI: 40,128-40,212)	55.4	Add DS-TB and RR cases diagnosed (see Tables 2 and 3 for estimates).	• DS-TB: 39,549 (95%CI: 39,501-39,585) • RR-TB: 627
Gap 3	3,745 (95%CI: 3,697-3,781)	5.2	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated	36,431	50.3	Add DS-TB and RR cases notified and treated (see Tables 2 and 3 for estimates).	• DS-TB: 35,922 • RR-TB: 509
Gap 4	3,731	5.1	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated	32,700	45.1	Add DS-TB and RR cases successfully treated (see Tables 2 and 3 for estimates).	• DS-TB: 32,304 • RR-TB: 396

[1]Estimate from: World Health Organization. Tuberculosis data. Available from: https://www.who.int/teams/global-tuberculosis-programme/data.

Table 2a. Drug-susceptible TB Care Cascade in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. Overall TB burden	70,755 (40,009-107481)	100	Overall TB burden minus RR-TB cases.	• TB burden: 72,495 (40,495-111,495) • RR cases: 1740 (486-4014)
Gap 1	28,278 (0-63,856)	40.0	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	42,477 (95%CI: 41,614-43,625)	60.0	Add the number of missed cases to the total number of DS-TB cases diagnosed (step 3). Missed cases estimated based upon TB test sensitivity by HIV-status, corrected for the number of patients with negative TB tests who were empirically treated (Table 2b).	• Number diagnosed: 39,549 (95%CI: 39,501-39,585) • Number missed: 2,928 (95%CI: 2,112-4,040)
Gap 2	2,928 (95%CI: 2,112-4,040)	4.1	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	39,549 (95%CI: 39,501-39,585)	55.9	Back calculated from number of cases notified and proportion of patients lost-to-follow-up prior to initiation of TB therapy. Pre-treatment LTFU estimated based on difference between number of microbiologically confirmed DS PTB cases detected and number of microbiologically confirmed DS PTB cases notified (Table 2c).	• Pre-treatment LTFU estimate: = 9.2 (95%CI: 9.1-9.3) • Number of patients notified in 2018: 35,922
Gap 3	3,627 (95%CI: 3,579-3,663)	5.1	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	35,922	50.8	Exact value from aggregated facility-level TB notification data.	• All patients with DS-TB who were notified and started on treatment (including new, relapse, treatment after failure, treatment after loss-to-follow-up patients and other previously treated cases).
Gap 4	3,618	5.1	Step 4 estimated cases minus Step 5 estimated cases	
Step 5. Successfully treated for TB.	32,304	45.7	Exact value from aggregated facility-level TB treatment outcomes data.	• All patients with DS-TB who successfully completed TB therapy (including new, relapse, treatment after failure, treatment after loss-to-follow-up patients and other previously treated cases).

Table 2b. Estimation method for determining number of patients with DS-TB who accessed TB testing in 2018

Variable	HIV-positive	HIV-negative	Overall
Total number of all microbiologically-confirmed TB cases (who therefore underwent microbiological tests)[1]	8,025 (PTB) + 320 (EPTB) = 8,345	9,803 (PTB)+1,137 (EPTB) = 10,940	19,285
Number of the above who underwent Xpert[1]	7,320	9,071	16,391
Number who underwent smear[1]	1,025	1,869	2,894
Proportion who underwent smear only (were smear-positive but Xpert either not done, or negative)[2]	96.9% (95%CI: 95.6-98.0)	98.1% (95%CI: 97.1-98.8)	97.7% (95%CI:96.9-98.3)
Number who underwent smear only	1,025 x .969% (95%CI: .956-.980) = 993 (95%CI: 980-1,005)	1,869 x .981% (95%CI: .971-.988) = 1,833 (95%CI: 1815-1,847)	-
Sensitivity of Xpert[3]	81% (95%CI 75-86)	88% (95%CI: 83-92)	85% (95%CI: 82-88)
Cases missed by Xpert	7,320/ .81 (95%CI .75-.86) - 7,320 = 1,717 (95CI: 1,192-2,440)	9,071 /.88 (95%CI: .83-.92)- 9,071 = 1,237 (95%CI: 789-1,858)	2,594 (95%CI: 1,980-4,298)
Sensitivity of smear microscopy[4,5]	50% (95%CI:42-57)	76% (95%CI: 70-80)	-
Cases missed by smear	993/0.50 (95%CI:0.42-0.57)- 993 = 1,025 (95%CI: 773-1,415)	1,833/0.76 (0.70-0.80)-1,833 = 590 (95%CI: 467-801)	1,615 (95%CI: 1,240-2,216)
Total combined cases missed by Xpert and smear	2,472 (95CI: 1,965-3,855)	1,827 (95%CI: 1,256-2,659)	4,569 (95%CI: 3,221-6,514)
Proportion of patients who had a negative Xpert that were empirically treated[2]	30.6% (95%CI: 28.6-32.7)	22.7% (95%CI:19.8-25.9)	28.9 (95%CI: 27.2-30.6)
Negative Xpert / received empiric therapy	1,717 (95CI: 1,192-2,440) x .306 (95%CI: .286-.327) = 525 (95: 341-798)	1,237 (95%CI: 789-1,858) x .227 (95%CI:.198-259) = 281 (95%CI: 156-481)	806 (95%CI: 497-1,279)

Proportion of patients who had a negative smear that were empirically treated[2]	58.9% (95%CI: 56.8-61.0)	39.2% (95%CI: 36.9-41.4)	50.1 (95%CI 48.5-51.6)
Negative smear / received empiric therapy	1,025 (95%CI: 773-1,415) x .589 (95%CI: .568-.610) = 604 (95%CI: 439-863)	590 (95%CI: 467-801) x .392% (95%CI: .369-.414) = 231 (95%CI: 172-332)	835 (95%CI: 612-1,195)
Total cases that were negative by Xpert or smear that were empirically treated	1,129 (95%CI: 780-1,661)	529 (95%CI: 329-813)	1,641 (95%CI: 1,109-2,474)
Total Missed cases (Total number of cases missed by Xpert or smear minus those were empirically treated)	1,613 (95%CI: 1,185-2,194)	1,315 (95%CI: 927-1,8460	2,928 (95%CI: 2,112-4,040)

[1]Exact value from 2018 national TB laboratory register, [2]Estimate from: individual-level TB notification data from 4 provinces in 2017, n=11,814 (unpublished), [3]Estimate from: Horne DJ, Kohli M, Zifodya JS, et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2019 Jun 7;6(6):CD009593.[4]Estimate from: Boehme CC, Nicol MP, Nabeta P, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. Lancet 2011; 377:1495–505. [5]Estimate from: Steingart KR, Henry M, Ng V, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis 2006;6:570–81.

Table 2c. Estimation method for determining proportion of patients with pre-treatment lost-to-follow-up.

Variable	Overall
Unadjusted number of microbiologically-confirmed pulmonary TB cases[1]	19,285 (16,391 Xpert and 2,894 smear)
Proportion of patients with positive smear who also have a positive Xpert result[2]	2.3% (95%CI 1.7-3.1)
Number of patients with positive smear who also have a positive Xpert result[2]	2,894 x .023% (95%CI .017-.031) = 67 (95%CI: 49-90)
Adjusted number of microbiologically-confirmed PTB cases	(2,894 - 67 (95%CI: 49-90)) + 19,218 (95%CI: 19,195-19,236)
Number of patients with microbiologically-confirmed pulmonary TB notified in 2018[3]	17,456
Proportion of all patients with microbiologically-confirmed TB who were registered and started TB treatment	90.8 (95%CI: 90.7-90.9)
Pre-treatment lost-to-follow-up (LTFU) estimate:	100% - 90.8 (95%CI: 90.7-90.9) = 9.2% (95%CI: 9.1-9.3)

[1]Exact value from 2018 nationally aggregated TB laboratory register, [2]Estimate from: individual-level TB notification data from 4 provinces in 2017, n=11,814 (unpublished).[3]Exact value from 2018 nationally aggregated TB notification register.

Table 3. Rifampicin resistant TB Care Cascade in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. Overall TB burden	1,740 (486-4,014)	100	Overall TB burden multiplied by estimated proportion of cases with rifampicin resistance.	• TB burden: 72,495 (40,495-111,495) • Overall estimate of RR-TB: 2.4% (95CI: 1.2-3.6)[1]
Gap 1	830 (range, 0-2,921)	47.7	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	910 (95%CI: 776-1,093)	52.3	Back calculated from RR tuberculosis cases diagnosed on the basis of cases bacteriologically diagnosed, by test type and test sensitivity.	• RR-TB cases diagnosed: 627 • RR-TB cases missed: 283
Gap 2	283 (95%CI: 149-466)	16.3	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	627	36.0	Exact value from aggregated facility-level TB laboratory data.	• All patients with microbiologically-confirmed RR-TB
Gap 3	118	6.8	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	509	29.3	Exact value from aggregated facility-level TB notification data.	• All patients with RR-TB who were notified and started on treatment.
Gap 4	113	6.5	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated for TB	396	22.8	Exact value from aggregated facility-level TB treatment outcomes data.	• The number of RR-TB who were notified and started on treatment who were successfully treated.

[1]Estimate from: Kapata N, Mbulo G, Cobelens F, et al. The Second Zambian National Tuberculosis Drug Resistance survey - a comparison of conventional and molecular methods. *Trop Med Int Health*. 2015;20(11):1492-1500. This is the most recent Zambia national drug resistance survey. A higher estimate utilizing MDR-TB Plus chosen because it more closely coincides with WHO RR-TB incidence estimates for 2018.

Table 3b. Estimation method for determining number of patients with RR-TB who accessed TB testing in 2018

Variable	HIV-positive	HIV-negative	Overall, No
Number of laboratory-confirmed RR-cases	-	-	627
Proportion of RR-TB patients notified in 2018, by HIV-status.[1]	59.1% (95CI: 54.6-63.6)	40.9% (95%CI: 36.4-45.4)	-
Number of RR-TB patients diagnosed in 2018, by HIV-status	627 x 59.1% (95CI: 54.6-63.6) = 371 (95%CI: 342-399)	627 x 40.9% (95%CI: 36.4-45.4) = 256 (95%CI: 228-285)	627
Number of RR-cases detected by Xpert	-	-	372
Number of RR-cases detected by Xpert, by HIV-status	372 x 59.1% (95CI: 54.6-63.6) = 220 (95%CI: 203-237)	372 x 40.9% (95%CI: 36.4-45.4) = 152 (95%CI: 135-169)	372
Combined sensitivity of Xpert for Rif-Resistance, by HIV status[2]	• Sensitivity of Xpert for TB: 81% (95%CI: 75% to 86%) • Sensitivity of Xpert for RIF-resistance: 96% (94% to 97%) • Overall sensitivity for RR-TB: 77.8% (95%CI 70.5-83.4)	• Sensitivity of Xpert for TB: 88% (95%CI: 83% to 92%) • Sensitivity of Xpert for RIF-resistance: 96% (94% to 97%) • Overall sensitivity for RIF-resist TB: 84.5% (95%CI 78.0-89.2)	-
RR-cases missed by Xpert	220 (95%CI: 203-237)/ .778 (95%CI .705-.834) – 220 = 63 (95%CI: 24-116)	152 (95%CI: 135-169)/ .845 (95%CI .780-.892) – 152 = 28 (95%CI: 0-64)	91 (95%CI: 23-180)
Number of RR-cases detected by MDR-TB plus	-	-	135
Number of RR-cases detected by MDR-TB plus, by HIV-status	135 x 59.1% (95CI: 54.6-63.6) = 80 (95%CI: 74-86)	135 x 40.9% (95%CI: 36.4-45.4 = 55 (95%CI: 49-61)	135
Combined sensitivity of MDR-TB plus*[3]	• Sensitivity of smear for TB: 50% (95%CI:42-57) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of MDR-TB plus: 96.9% (95CI%:95.5-98.0) • Overall sensitivity for RR-TB: 48.5% (95%CI: 40.1-55.9)	• Sensitivity of smear for TB: 76% (95%CI: 70-80) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of MDR-TB plus: 96.9% (95CI%:95.5-98.0) • Overall sensitivity for RR-TB: 73.6% (95%CI: 66.9-78.4)	-
RR-cases missed by MDR-TB plus	80 (95%CI: 74-86) /.485 (95%CI: .401-.559) - 80 = 85 (95%CI: 52-134)	55 (95%CI: 49-61) / .736 (95%CI: .669-.784) - 55 = 20 (95%CI: 7-36)	105 (95%CI: 59-171)

Number of RR-cases detected by liquid culture (MGIT 960)*[4]			120
Number of RR-cases detected by liquid culture (MGIT 960)*[4], by HIV-status	120 x 59.1% (95CI: 54.6-63.6) = 71 (95%CI: 66-76)	120 x 40.9% (95%CI: 36.4-45.4 = 49 (95%CI: 44-54)	120
Combined sensitivity of liquid culture	• Sensitivity of smear for TB: 50% (95%CI:42-57) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of liquid culture for RR-TB: 99.2% (95%CI: 95.9-100) • Overall sensitivity for RR-TB: 49.6% (40.3-57.0)	• Sensitivity of smear for TB: 50% (95%CI:42-57) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of liquid culture for RR-TB: 99.2% (95%CI: 95.9-100) • Overall sensitivity for RR-TB: 75.4 (95%CI: 67.1-80.0)	-
RR-cases missed by liquid culture	71 (95%CI: 66-76) / .496 (95%CI: .403-.570) – 71 = 72 (95%CI: 61-83)	43 (95%CI: 49-54) / .754 (95%CI: .671-.800) – 43 = 16 (95%CI: 6-32)	88 (95%CI: 67-115)
Total microbiologically-missed cases	63 (95%CI: 24-116) + 85 (95%CI: 52-134) + 72 (95%CI: 61-83) = 220 (95%CI: 137-333)	28 (95%CI: 0-64) + 20 (95%CI: 7-36) + 16 (95%CI: 6-32) = 64 (95%CI: 13-133)	283 (95%CI: 149-466)
Received empiric therapy*	0	0	0
Total Missed cases	220 (95%CI: 137-333)	64 (95%CI: 13-133)	283 (95%CI: 149-466)

[1]Exact value from 2018 national TB laboratory register. [2]Estimate from: Horne DJ, Kohli M, Zifodya JS, et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2019 Jun 7;6(6):CD009593. [3]Estimate from: WHO. The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin. Geneva: WHO; 2016. Available at: https://apps.who.int/iris/bitstream/handle/10665/250586/9789241511261-eng.pdf?sequence=1, [4]Estimated from: Tortoli E, Benedetti M, Fontanelli A, Simonetti MT. Evaluation of automated BACTEC MGIT 960 system for testing susceptibility of Mycobacterium tuberculosis to four major antituberculous drugs: comparison with the radiometric BACTEC 460TB method and the agar plate method of proportion. *J Clin Microbiol.* 2002;40(2):607-610.

Table 4. Drug-susceptible TB Care Cascade among HIV-positive individuals in Zambia in 2018

Variable	Cases, range	Proportion (%), range	Estimation method	Calculation
Step 1. Overall TB burden	43,411 (23,911-65,911)	100	WHO 2019 analysis of TB incidence in 2017 plus 50% of the number of undetected cases from 2018.[1]	• TB incidence, 2018 (all): 36,000 (range, 23,000-51,000) • TB incidence, 2017 (all): 36,000 (range, 23,000-51,000) • Case detection rate, 2017: 58.8% (range, 41.5-92.1) • Estimated undetected cases 2017: 14,822 (range, 1,822-29,822) • 50% of undetected cases who have not died/self-cured: 7,411 (range, 911-14,911)
Gap 1	18,597 (0-40,495)	43.0	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	24,746 (95%CI: 24,290-25,349)	57.0	Add the number of missed cases of DS-TB among HIV-positive individuals to the total number of DS-TB cases diagnosed among HIV-positive individuals (step 3). Missed cases estimated based upon TB test sensitivity in HIV-positive individuals, corrected for the number of patients with negative TB tests who were empirically treated (Table 2b).	• Number diagnosed: 23,133 (95CI: 23,106-23,154) • Number missed (table 2b): 1,613 (95%CI: 1,185-2,194)
Gap 2	1,613 (95%CI: 1,185-2,194)	3.7	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	23,133 (95%CI: 23,106-23,154)	53.3	Back calculated from number of cases notified and proportion of patients lost-to-follow-up prior to initiation of TB therapy [see Table 2c]; [assumed to be the same independent of HIV-status].	• Pre-treatment LTFU estimate: 9.2% (95%CI: 9.1-9.3) • Number of HIV-positive patients notified in 2018: 21,012 (95%CI: 20,962-21,064)
Gap 3	2,121 (95%CI: 2,094-2,142)	4.9	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	21,012 (95%CI: 20,962-21,064)	48.4	Exact value from aggregated facility-level TB notification data adjusted for proportion of patients without an HIV test.	• DS-TB: 19,332 • Proportion of all notified patients who had an HIV test: 94.9% (95%CI: 94.6-95.1)

Gap 4	2,433 (95%CI: 2,337-2,529)	5.6	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated for TB	18,579 (95%CI: 18,535-18,625)	42.8	Exact value from aggregated facility-level TB treatment outcomes data (number successfully treated) adjusted for proportion of patients without an HIV test.	• DS-TB: 17,624 • Proportion of all notified patients who had an HIV test: 94.9% (95%CI: 94.6-95.1)

[1]Estimate from: World Health Organization. Tuberculosis data. Available from: https://www.who.int/teams/global-tuberculosis-programme/data.

Table 5. Drug-susceptible TB Care Cascade among HIV-negative individuals in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. Overall TB burden	27,344 (16,098-41,570)	100	Total number of DS-TB cases minus number of DS-TB cases among HIV-positive individuals	• Number of DS-TB cases: 70,755 (range, 40,009-107,481) • Number of HIV-positive DS-TB cases: 43,411 (23,911-65,911)
Gap 1	10,939 (98-24,620)	35.2	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	17,731 (95%CI: 17,324-18,276)	64.8	Total number of DS-TB cases who accesses TB tests minus the number of DS-TB cases who accessed TB tests among HIV-positive individuals	• Number of DS-TB cases that accessed tests: 42,477 (95%CI: 41,614-43,625) • Number of HIV-positive DS-TB cases diagnosed: 24,746 (95%CI: 24,290-25,349)
Gap 2	1,315 (95%CI: 927-1,846)	4.8	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	16,415 (95%CI: 16,395-16,431)	60.0	Total number of DS-TB cases diagnosed minus the number of DS-TB cases diagnosed among HIV-positive individuals	• Number of DS-TB cases diagnosed: 39,549 (95%CI: 39,501-39,585) • Number of HIV-positive DS-TB cases diagnosed: 23,133 (95%CI: 23,106-23,154)
Gap 3	1,505 (95%CI: 1,486-1,520)	5.5	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	14,910 (95%CI: 14,858-14,960)	54.5	Total number of DS-TB cases notified minus the number of DS-TB cases among HIV-positive individuals notified	• Number of DS-TB cases notified: 35,922 • Number of HIV-positive DS-TB cases notified: 21,012 (95%CI: 20,962-21,064)
Gap 4	1,185 (95%CI: 1,089-1,281)	4.3	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated for TB	13,725 (95%CI: 13,679-13,769)	50.2	Total number of DS-TB cases successfully treated minus the number of DS-TB cases among HIV-positive individuals successfully treated	• Number of DS-TB cases treated: 32,304 • Number of HIV-positive DS-TB cases treated: 18,633 (95%CI: 18,535-18,725)